

**Remarks**

This Amendment is submitted to place the case in better condition for appeal or allowance; entry of the above amendments and reconsideration of the application in view of the amendments and remarks herein are respectfully requested.

Claims 1-16 and 26-30 are in the application. Claims 5, 6, 13 and 16 (in part) have been withdrawn from consideration by the Examiner; claims 5, 6 and 13 have been canceled and claim 16 has been amended herein. Claims 1-3, 16 and 26-30 have been rejected and claims 4, 7-12 and 14-15 has been objected to; claim 26 has been canceled and claims 27-30 have been amended herein.

The Examiner has stated that non-elected subject matter remains in claim 16; that non-elected subject matter has been canceled by the above amendment to claim 16. Applicants reserve the right to pursue the canceled subject matter in another application. Claim 16 is now believed to be in condition for allowance.

The Examiner has also stated that the subject matter of claims 5, 6, and 13 are outside the scope of the elected invention; these claims have been canceled herein. Applicants reserve the right to pursue the canceled subject matter of these claims in one or more divisional or continuation applications.

The Examiner has noted that claims 26-30 depend on a canceled claim. Applicants have canceled claim 26 as being redundant in view of the amendment to claim 16, and have amended claims 27-30 to depend on claim 16. These claims are now deemed in condition for allowance.

Claims 1, 2, 16 and 26-30 have been rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter not described in the specification in an enabling manner. Specifically, the Examiner has said that the specification does not teach how to make and use all the claimed compounds. Applicants traverse this rejection.

Applicants' specification clearly teaches how to make compounds of the present invention. Applicants cannot be expected to describe or illustrate how to make each individual compound claimed. Those starting materials for which a method of making are not described are readily available and/or a method for making them is known to those skilled in the art. One of ordinary skill in the art would readily understand how to make the compounds of the invention from the disclosure in the specification.

The Examiner has not pointed out any specific starting material or claimed compound for which the description allegedly is insufficient to teach how to make or use; consequently, Applicants are unenlightened as to the exact difficulty the Examiner envisions for one skilled in the art who wishes to follow the teachings of the specification. Applicants believe that the detailed description and examples of the specification would allow one of ordinary skill to practice the invention without

undue experimentation. For these reasons, and in the absence of evidence to the contrary, the instant rejection should be withdrawn, and Applicants hereby respectfully request the withdrawal thereof.

Claims 1-3 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Abou-Gharbia (5,254,552) in view of Cliffe (5,420,278). The Examiner has stated that for compounds where  $m=0$  the cited art does not suggest the claimed compounds, but where  $m=1$  the claimed compounds are obvious. The Examiner also has stated that the cited art provides sufficient motivation to employ phenyl in place of hydrogen in the closest compound of Abou-Gharbia ('552) and its preparation would be well within the ordinary skill in the art. The Examiner has stated further that Abou-Gharbia teaches the adamantyl acyl chloride is available and that when this is coupled with the amine of example 37 of Cliffe the instant product results. Applicants traverse this rejection.

Abou-Gharbia '552 describes compounds which differ structurally from those claimed by Applicants. All of the reference compounds lack the Applicants' YR<sub>1</sub> group in the location it occupies in the claimed compounds. Additional differences from the claimed compounds include: the alkyl chain between the piperazine and the carboxamide group may be 2-5 carbon atoms long; the group on the other side of the carboxamide group may vary considerably in both the alkyl and cyclic portions thereof; and, the N of the carboxamide may be substituted, which is not permitted in Applicants' compounds. By selecting the "right" choice for each of these variables, using the Applicants' invention as a guide, the Examiner has identified compounds that differ from some of Applicants' compounds by virtue of lacking the YR<sub>1</sub> group. Nevertheless, even these compounds are not compounds of the claimed invention, as the Examiner has conceded. This reference clearly does not teach or suggest the claimed invention.

Cliffe '278 describes piperazine compounds which differ from some of the claimed compounds at least in that the adamantyl or noradamantyl group is replaced by a different group. However, the most preferred reference compounds (see reference column 2, lines 52-64) are those wherein an ethyl chain is attached to a -CO<sub>2</sub>R<sup>6</sup> ester group or a -CONR<sup>5</sup>R<sup>9</sup> amide group, whereas in the claimed compounds the ethyl is attached to an -NCO-(nor)adamantyl group. Furthermore, in the preferred reference compounds the NR<sup>5</sup>R<sup>9</sup> group forms a cyclic compound that includes the N, rather than having a separate cyclic group attached to the amide group. Therefore, not only is there no (nor)adamantyl group in the reference compounds, but the reference teaches that the preferred compounds do not have the same atoms, or the same arrangement of atoms in the central chain as do the presently claimed compounds. Using the Applicants' invention as a guide, the Examiner has selected those (non-preferred) reference compounds which are closest to the claimed compounds, which the Examiner has admitted are not compounds claimed by Applicants. This reference clearly does not teach or suggest the claimed invention.

Having used Applicants' invention as a guide to select those compounds within the broad genus of each reference which are closest to Applicants' claimed compounds, the Examiner concluded

that it would have been obvious to replace the alpha hydrogen on the compounds of Abou-Gharbia '552 with the phenyl group taught by Cliffe '278 to obtain the instant invention, with the expectation that the compounds would have the properties claimed by Applicants. The Examiner has chosen not to enlighten us at to why this particular substitution would be obvious to make, rather than some other substitution, for example, replacing the adamantyl of the '552 patent with the preferred group from the '278 patent.

The Examiner apparently has carefully studied the various compounds in Cliffe and discovered that, although the preferred compounds of Cliffe are not very close to the claimed compounds, there is a non-preferred compound in Cliffe Example 37 which differs from one of the claimed compounds in that it contains a cyclohexyl group instead of an adamantyl group. Having selected this compound, the Examiner has concluded that it would be obvious to use adamantyl acyl chloride to transform the cyclohexyl compound into the corresponding adamantyl compound. What the Examiner has not said is where in the art the selection of this Cliffe compound and subsequent its reaction with adamantyl acyl chloride are taught or suggested. Applicants respectfully submit that no such teachings or suggestions exist in the cited art.

With the Applicants' invention as a guide, the Examiner has selected a non-preferred embodiment from example 37 of the Cliffe patent which has a phenyl sidechain and a compound in Abou-Gharbia that is closest to the claimed compounds, and has concluded that it is obvious to place a phenyl sidechain in the corresponding location in the closest compound of Abou-Gharbia. A major flaw in this reasoning is that the prior art suggests neither selecting these particular compounds, nor making the substitution suggested by the Examiner, nor how to make that substitution. In fact, Cliffe says that other compounds are preferred. corresponding to the claimed compounds, a compound of the present invention would not result. The test for obviousness is not whether one armed with Applicants' teaching can find similar compounds and figure out how to reconstruct the invention, but rather, at the time the invention was made would the prior art clearly guide or motivate one of ordinary skill in the art (who does not have knowledge of Applicants' invention) to try to make the invention and teach that person how to do so. In this case, the answer is no. One considering all the prior art without knowledge of Applicants invention would have no reason to make the particular selections the Examiner has indicated, and would not be informed by the prior art how to make the compounds.

If one skilled in the art were considering Cliffe, would one select the compound of Example 37 rather than the preferred compounds, if one were not trying to recreate the claimed invention? Would one select from Abou-Gharbia the compound closest to the claimed compounds, if one were not trying to recreate the claimed invention? Would one select the phenyl substituent of the Cliffe compound as the element to use to alter the compound of Abou-Gharbia, if one were not trying to recreate the claimed invention? Does the prior art provide specific motivation to do any of these

things, let alone all of them, absent knowledge of the claimed invention? Applicants believe that the answer to all these question is negative and, consequently, that the invention is not obvious from the teachings of the cited art.

Applicants respectfully submit that the Examiner has engaged in a classic exercise of hindsight reasoning. At every step in the Examiner's analysis, Applicants invention has been used as a guide to select the "right" pieces with which to assemble the invention. The Examiner has failed to explain, or even hint, at where in the references one skilled in the art would find the motivation or guidance to make all the "right" choices for each genus, and further to combine the reference teachings to make the one substitution in the compounds of the '552 patent that would produce the Applicants' invention. Logically, one would assume that one considering the '278 patent would look toward the preferred compounds described therein, rather than the compounds closest to the present invention. However, with the Applicants' teaching as a guide the Examiner set out to reconstruct the invention from prior art, and that provided the necessary guidance to make all the "right" choices. This guidance, however, does not exist in the prior art. Consequently, Applicants respectfully submit that the present invention would not have been obvious to those skilled in the art at the time the invention was made, absent knowledge of the present invention.

An additional and separate reason that Applicants' invention would not have been obvious to one skilled in the art who did not have the benefit of Applicants' teaching, is that the skilled practitioner could not predict that the claimed compounds would function as they do. The present invention comprises compounds that have agonist or partial agonist activity and thus are useful for treating neurodegeneration; no such use or activity is found in the cited references. At best, even using the Examiner's hindsight analysis to obtain the compounds, it may have been obvious to try these compounds for some of the claimed uses (but not for treating neurodegeneration); that is not a sufficient basis for an obviousness rejection.

A further separate basis for finding that the invention is not obvious is that the prior art does not teach one how to make the compounds of the present invention. To make the invention obvious, the prior art must contain sufficient teachings to enable one skilled in the art to make the invention. Compounds which have different structures require different starting materials and, even when the structures seem very similar, an entirely different synthesis route may be needed. Therefore, the method for making the structurally different compounds must be clear from the prior art. The Examiner has not shown that to be the case here. If the Examiner believes that the method of making the claimed compounds is obvious form the cited art, Applicants' respectfully request that the Examiner explain where in the cited art the requisite teaching is found.

For all the foregoing reasons, Applicants find that the cited references, whether taken individually or in combination, do not teach or suggest the claimed invention, and Applicants respectfully request withdrawal of the rejection of claims 1-3 under 35 U.S.C. § 103(a).

Claims 4, 7-12 and 14-15 have been objected to as being dependent on a rejected claim, but has been deemed to cover patentable subject matter, and would be allowed if rewritten in independent form. Applicants thank the Examiner for noting that his claim covers patentable subject matter. However, in view of the foregoing arguments and amendments, Applicants believe that claims 4, 7-12 and 14-15 are each dependent on a patentable claim and do not need to be rewritten in independent form. Therefore, this objection is deemed moot.

In view of the amendments and remarks contained herein, Applicants respectfully request withdrawal of all the instant rejections and objections

In view of the amendments and arguments made herein, Applicants believe that all of claims 1-4, 7-12, 14-16 and 27-30 are patentable and respectfully solicit the allowance of these claims at an early date. If the Examiner disagrees, it is respectfully requested that the above amendments be entered, to place the application in better condition for appeal. The amendments contained herein merely cancel subject matter in the claims and do not raise any new issues which require additional examination.

No fees are believed to be due herewith; however, if a fee is required it may be charged to Deposit Acct. No. 01-1425. An extension of time is not believed to be needed, but if needed, please consider this a request therefor and charge the required fee to the aforesaid deposit account.

  
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**Version With Markings To Show Changes Made**

--16 (Amended). A method for treating [neurodegenerative disorders] stroke comprising administering a therapeutically effective amount of a compound of Claim 1 or a pharmaceutical salt thereof, to a patient in need of said treatment.--

--27 (Amended). The method of claim [26] 16 wherein stroke is thromboembolic stroke.--

--28 (Amended). The method of claim [26] 16 wherein stroke is focal ischemia.--

--29 (Amended). The method of claim [26] 16 wherein stroke is global ischemia.--

--30 (Amended). The method of claim [26] 16 wherein stroke is transient ischemic attack.--

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